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Infarma CIÊNCIAS FARMACÊUTICAS

Revisão

Caffeine intake almost always affects physical performance and cognitive processes responsible for awareness

A ingestão de cafeina pode afetar a performance física e os processos cognitivos responsáveis pela consciência

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ABSTRACT

Sports foods and supplements can play a significant role in the sports nutrition plans of high-level athletes. It has been found that taking specific dietary supplements can have ergogenic and performance-enhancing effects. Over the past two decades, there have been no major changes in the recommendations for caffeine supplementation. However, scientific knowledge has been significant in recent times, such that the state of the art needs to be updated. This study aims to confirm that caffeine (1,3,7-trimethylxanthine), a substance found in beverages such as coffee, tea and energy drinks, can be both an ergogenic support for individuals engaged in physical activity and an effective cognitive support. In this context, this review outlines the current framework of knowledge. The relationship between the uses and effects of caffeine in power and endurance sports has been demonstrated. In order to achieve and maintain the high levels of performance required in sporting events, planning proper sports diet supplementation can only strengthen and revitalize athletes after strenuous training. Furthermore, the effects of caffeine intake on the state of alertness have been evaluated in the military as well. Significant physical performance, such as marching over rough terrain, sometimes with very heavy loads, may be required during military training and tactical operations. In addition, operational situations with reduced or sleep deprivation may occur.Thus, several studies argue that genetic background, diet, gender identity and hormonal status have a bearing on the absorption, metabolism and physiological and functional effects of caffeine. Regarding the key points - individualized dosages and timing of caffeine intake - it would be desirable to go further with the studies to optimize the effects of caffeine.

Keywords: Central Nervous System stimulants; dietary supplements; genetic background; military personnel; performance-enhancing substances; physical functional performance.

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RESUMO

Nas últimas duas décadas, não houve grandes mudanças nas recomendações de suplementação com cafeína. No entanto, o avanço do conhecimento científico tem sido significativo nos últimos tempos, de forma que o estado da arte precisa ser atualizado. Alimentos e suplementos esportivos podem desempenhar um papel importante nos planos de nutrição esportiva de atletas de alto nível. Ingerir suplementos dietéticos específicos pode ter efeitos ergogênicos e de melhoria do desempenho. Este estudo visa confirmar que a cafeína (1,3,7-trimetilxantina), substância encontrada em bebidas como café, chá e bebidas energéticas, pode ser tanto um suporte ergogênico para indivíduos praticantes de atividade física quanto um suporte cognitivo eficaz. Neste contexto, esta revisão delineia o atual quadro de conhecimento. Vários estudos têm demonstrado que o histórico genético, a dieta, a identidade de gênero e o status hormonal influenciam a absorção, o metabolismo e os efeitos fisiológicos e funcionais da cafeína. O planejamento adequado da suplementação da dieta esportiva só pode fortalecer e revitalizar os atletas após treinamento extenuante para alcançar e manter os altos níveis de desempenho exigidos em eventos esportivos. A relação entre os usos e efeitos da cafeína em esportes de força e resistência foi demonstrada. Enquanto isso, os efeitos da ingestão de cafeína no estado de alerta também foram avaliados em militares. Por exemplo, pode acontecer que um desempenho físico significativo seja exigido durante o treinamento militar e operações táticas, como marchar em terrenos acidentados, às vezes com cargas muito pesadas. Além disso, podem ocorrer situações operacionais com redução ou privação do sono.

Palavras-chave: estimulantes do Sistema Nervoso Central; suplementos alimentares; antecedentes genéticos; pessoal militar; substâncias que melhoram o desempenho; desempenho funcional físico.

INTRODUCTION

In recent decades, the increasing competitiveness in sports has contributed to the search for the best training and nutrition conditions for high-level professional athletes. From simply expressing energy needs, sports nutrition has evolved into a well-calibrated nutritional plan for athletes that enables them to make their sports project achievable. Supporters, the media, and the sports industry push athletes to improve performance through complicated workouts, proper nutrition, and dietary supplementation. Combining these factors can lead to ideal body composition results, optimal recovery time, and improved performance. According to research (1), there is some good and strong evidence that taking specific dietary supplements can have ergogenic effects and improve athletes' performance. Six dietary supplements, such as β-alanine, sodium bicarbonate, creatine, glycerol, beet juice, and caffeine, are considered ergogenic aids based on the demonstrated level of scientific evidence. Not only has it been shown that taking specific dietary supplements can have ergogenic and performance-enhancing effects, but caffeine (1,3,7-trimethyl xanthine), a substance found in beverages such as coffee, tea, and energy drinks, is confirmed as a valuable cognitive aid during physical activity in training and tactical operations in a military context (2). In this paper, the focus is on new insights that have the potential to increase sports performance. In addition, the basics are recapitulated only when necessary and for reference, hoping to satisfy readers interested in the topic.

KEY MESSAGES

- Caffeine is proven to be among the legal performance-enhancing substances for both

functional and cognitive physical performance.

- The individual's genetic background is important in determining the response to caffeine in both men and women.
- Caffeine enhances cognitive information processing functions and vigilance under stressful conditions.
- Caffeine can help improve physical performance markers for both aerobic and activities with a predominantly anaerobic component.
- In the military, the high psycho-physical commitment component would appear to be enhanced by the ingestion of caffeine in various modes of administration.

GLOSSARY

BMI. The term 'BMI' refers to Body Mass Index. BMI is widely regarded as a diagnostic tool to assess a person's weight relative to normal or normal weight, statistically associated with a lower risk of getting sick from metabolic and other diseases. BMI = (weight expressed in kilograms) divided by (height, expressed in meters, squared).

CHO. In the literature, the term 'CHO' refers to carbohydrates. They are substances made up of carbon, hydrogen, and oxygen. They are part of the macronutrients, along with protein and fat. Carbohydrates provide 4 kilocalories (kcal) per gram. They consist of sugars (mainly glucose), starch, and dietary fibers.

PLA. The meaning of 'PLA' is the same as placebo. In pharmacology, it is an inert substance preparation that is administered primarily for the psychological effects it may have on the patient or to perform comparisons with effective drugs in a series of clinical trials.

BW and BM. The broad use of the term 'BW' is sometimes equated with 'BM'. Many authors considered indicate body weight, also known as body weight, by the abbreviation BW. According to The Oxford Dictionary of Sports Science & Medicine, body weight is the product of body mass (in kilograms) and acceleration due to gravity (approximately 9.81 m/s2) measured in newtons (N). In the other hand, according to other authors, body weight should be referred to as BM. BM is the abbreviation for body mass. By the Oxford Dictionary of Sports Science & Medicine, body mass in anthropometry is the mass of the human body measured to the nearest tenth of a kilogram.

CNS. Defined as the central nervous system, the CNS, according to the Cambridge Dictionary, is the main system of nerve control in a living thing, consisting of the brain and the main nerves connected to it.

METHOD

Several recent clinical studies have explored Factors that influence the efficacy and safety of caffeine in sport and other areas. And they represent the focus of this study. The collected studies were conducted on human volunteers. Before enrolling in the studies, all participants were fully informed of any risks and discomforts associated with the studies and gave written informed consent to participate. The investigations were approved by the Ethics Committees of the Universities involved by the latest version of the World Medical Association Declaration of Helsinki outlining ethical principles for medical research involving human subjects (3).

Review Framework. The review protocol is consistent with the objectives of this review of the recently published literature on caffeine, as the goal is to identify evidence for caffeine-induced effects of caffeine use in sports, as well as to examine the assumptions, patterns, and quality of published studies. To better appreciate the context, it would be deemed appropriate to provide an overview of the types of literature reviews. Usually, authors do database searches to identify, collect, and analyze available evidence on a topic of interest. It is noteworthy that narrative reviews, qualitative systematic reviews, quantitative systematic reviews, and scoping reviews differ in their characteristics, objectives, and purpose. The distinguishing features of a re-

view include the review question, the sources, the selection criteria, the evaluation and synthesis of the data, and the formulation of directions for practice. On a more specific note, a narrative review can be said to be a thorough and critical overview of previously published research on the author's specific topic of interest. Over time it has also been referred to as traditional review or literature review. It helps to establish a methodological framework for research. Like systematic reviews a narrative review evaluates, critiques and summarizes the available research on a topic, but is much less systematic and rigorous despite being evidence-based. Instead, a systematic review critically evaluates the literature that addresses a well-defined question topic. The PRISMA statement and the Cochrane protocol are the structured, predefined methods for evaluating and synthesizing relevant literature. A meta-analysis not only provides the best possible answer to the question, but also combines the results of all studies into a single statistical analysis. On the other hand, a qualitative systematic review assembles research on a topic by systematically searching for research evidence from primary qualitative studies and collating the results. Finally, a scoping review maps the size, characteristics or scope of the existing literature in a field of interest. It may act as a precursor to a systematic review.

Querying data. The data under study were extracted from archives of research publications for biomedical and health sciences. The search for relevant literature has been based on a methodology deemed appropriate. One was the search strategy on PubMed: caffeine AND sport AND performance OR cognitive AND military. Filters: Free full text, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, published in the last ten years (https://pubmed.ncbi.nlm.nih.gov/).

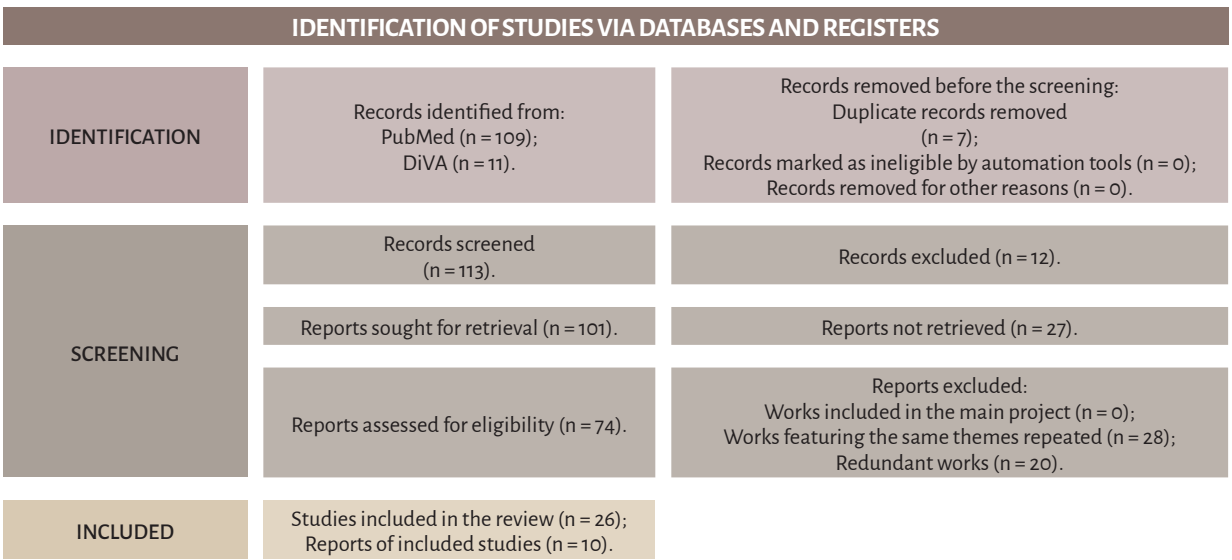
The other was the search strategy on DiVA (Digitala Vetenskapliga Arkivet): caffeine AND performance. Filters: Full text, Article in journal, Report, Doctoral thesis, Licentiate thesis, Conference paper, from 2008 to 2022 (https://www.diva-portal.org/smash/search.jsf?dswid=917).

The search of scientific databases has been carried out for about one year in 2022. The type of research design, publication date, sample size, and study duration were the key elements of the inclusion or exclusion criteria for all studies reviewed for this review. Grey literature, editorials, magazine articles and other forms of popular media were excluded. Studies focusing on programs for developing and improving athletic performance were selected by examining their title, abstract and full text. Then those relevant according to the predetermined criteria were admitted and included in this review. In addition, undesirable side effects of caffeine reported in the scientific articles reviewed were highlighted. And because of this systematic work, it has been possible to gradually broaden knowledge of the subject so as to offer a focused point of view. In summary, one hundred and twenty publications were identified, of which seventy-four were reviewed after the removal of duplicates and after the screening of title and abstract. After that, the final draft accurately reflects the remaining selected 26 studies that appear appropriate, relevant, and strictly limited to the purposes of this review. Table 1 shows the PICO (population, intervention, control and outcome) model used to survey the literature from scientific databases. Then the PRISMA diagram (Preferred Reporting Items for Systematic reviews and Meta-Analyses) is presented in Figure 1. Its purpose is to illustrate the details of the studies included in the assessment and to highlight their main findings. Overall, this review reaches several conclusions that are explained later in the text. And whether or not the studies considered have systematic bias, the importance of having had access to adequate evidence to ensure the quality of the studies is emphasized.

Table 1. The PICO (Population, Intervention, Comparison, and Outcome) tool approaches research from the perspective of logical and practical completeness of ideas.

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Sportspeople.	Sports nutrition plan with added ergogenic aids.	Sports nutrition plan without food supplements.	The added value of dietary supplementation with caffeine.

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart (PRISMA).



RESULTS AND DISCUSSION

A typical cup of coffee provides about 75-100 mg of caffeine. There is extensive literature on caffeine. It may be interesting for readers to have an up-to-date overview of the advantages and disadvantages of caffeine supplementation. Regarding caffeine consumption, according to EFSA, the European Food Safety Authority, caffeine is considered safe up to 400 mg per day when sourced from all food sources as part of a healthy, balanced diet (4). In recent decades, research has examined the effects of caffeine in several sports disciplines, especially concerning possible improvements induced in aerobic, anaerobic and mixed activities. Multiple, but sometimes divergent, confirmatory investigations support the claims asserted in the literature. While some studies on extreme environmental situations have evaluated whether caffeine supplementation leads to any benefit, other studies have looked at the particular scenarios that often occur in military missions. These typically require high levels of alertness, especially when fatigue looms (5). Depending on the context, noteworthy findings relate to the dosage and timing of caffeine ingestion, performance benefits, deferral of fatigue, and maintenance of an adequate level of alertness. The results of the reviewed studies have been evaluated and condensed to define the maximum development of current knowledge (Table 2). As is proper, the potential side effects that could result from ingesting caffeine were also mentioned. Ultimately, dietary supplementation with caffeine may be an effective strategy to support cognitive and physical performance in competitive and recreational sports, as well as to maintain an adequate state of alertness as needed.

Table 2. Details of a selection of included studies and key findings. (Please note: subject weight and height measures are intended as mean values of participants; NA stands for not available from source; for acronyms see Glossary).

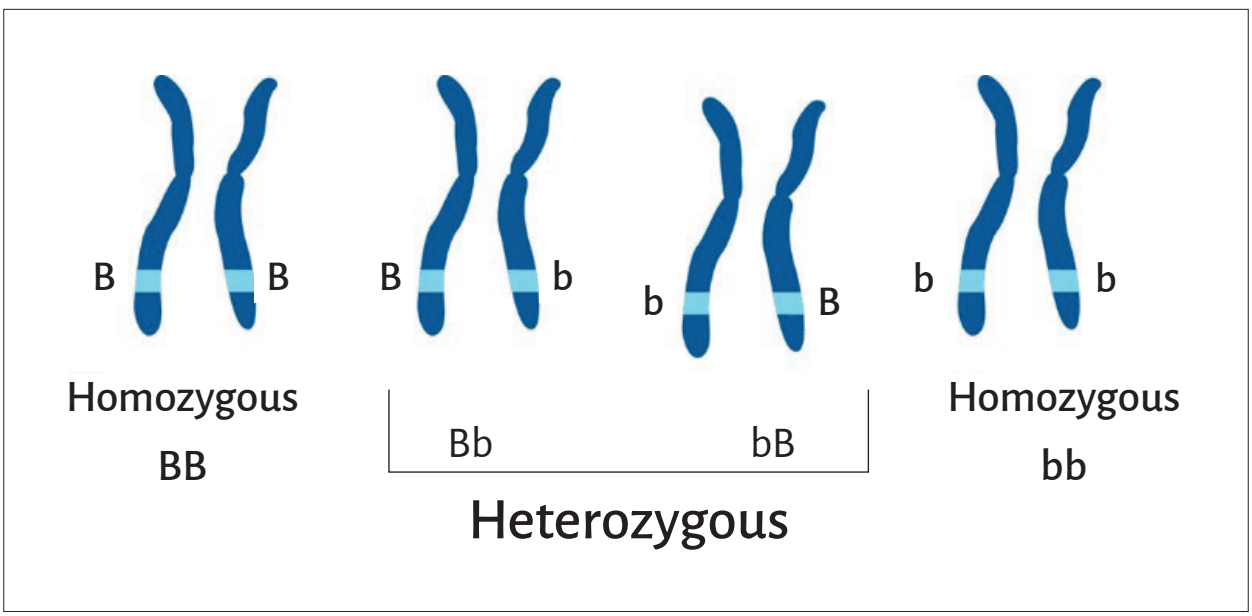
AUTHOR (YEAR), COUNTRY, (REFERENCE)	STUDY DESIGN	PARTICIPANTS	AGE	HEIGHT m	WEIGHT kg BMI (kg/m2) GENDER			PARTICIPANTS/ ACTIVITIES	CAFFEINE INTAKE COMPARED WITH PLACEBO	CONCLUSIONS
Carswell et al. (2020), UK,(13)	A double-blind, placebo-controlled crossover design.	12	24.0	1.78	74.7	NA	male	Physically active people.	3 mg·kg-1 BW	Caffeine improved cognitive performance in "fast metabolizer" CYP1A2 genotypes, whereas no differences emerged in performance on exercise.
		6	30.0	1.69	62.7	NA	female			
Grgicet al. (2020), Australia,(18)	A double-blind, randomized, crossover trial.	22	29.3	1.83	80.3	NA	male	Resistance-trained men.	3 mg·kg-1 BW	Carriers of the C allele of ADORA2A (rs5751876) indicated ergogenic responses to caffeine ingestion.
Grgicet al. (2020), Australia,(12)	A double-blind, randomized, crossover design.	AA group (n = 13)	27.0	1.82	78.2	NA	male	Resistance-trained men.	3 mg·kg-1 BW	Endurance-trained men may experience acute improvements in endurance, jumping, and sprinting exercise performance after caffeine ingestion. There were no significant differences in the effects of caffeine on exercise performance between individuals with the AA and AC/CC CYP1A2 genotypes.
		AC/CC group (n = 9)	29.8	1.83	80.9	NA	male			
Guestet al. (2018), Canada,(7)	A split-plot randomized, double-blinded, placebo-controlled design.	AA group (n = 49)	24.0	1.79	80.3	NA	male	Endurance sports (n = 100).	from 2 to 4 mg·kg-1 BW	Caffeine dosages of 2 and 4 mg·kg-1 BW improved 10-km cycling time in participants with the AA CYP1A2 genotype. Caffeine had no effect in those with the AC genotype and decreased performance at 4 mg·kg-1 BW in those with the CC genotype.
		AC group (n = 44)	25.0	1.77	79.7	NA	male	Power sports (n = 100).		
		CC group (n = 8)	25.0	1.81	92.9	NA	male	Mixed sports (n = 100).		

AUTHOR (YEAR), COUNTRY, (REFERENCE)	STUDY DESIGN	PARTICIPANTS	AGE	HEIGHT m	WEIGHT kg BMI (kg/m2) GENDER			PARTICIPANTS/ ACTIVITIES	CAFFEINE INTAKE COMPARED WITH PLACEBO	CONCLUSIONS
Keaneet al. (2020), Ireland,(8)	A double-blind, randomized design.	10	22.0	1.72	70.7	NA	male	Hurling players.	[Caffeine: 275 mg per serving] or [Caffeine: 200 mg per serving + CHO: 60 g per serving] versus [CHO only] or vs [PLA]	The combined intake of CHO + CAF had a significant effect on sprint performance during competitive hurling match simulations.
Kumaret al. (2015), USA,(24)	Design of clinical trials.	10	27.7	NA	NA	23.1	(10 male + 2 female)	Trained people.	3 mg·kg-1 BW	Exercise, when paired with caffeine, provided greater benefits to the attention task for accuracy, precision, and mental energy. However, the caffeine did not prevent a decline in mental energy or an increase in mental fatigue.
		10	26.8	NA	NA	23.7	(10 male + 2 female)	Sedentary people.	3 mg·kg-1 BW	
Laraet al. (2019), Spain,(27)	A crossover, double-blind, placebo-controlled experiment.	11	32.3	1.71	66.6	NA	(8 male + 3 female)	Healthy active individuals.	3 mg·kg-1 BW	The ergogenic effect of caffeine compared to placebo was greater on the first day of intake and then progressively decreased for 15-18 days; however, changes in the magnitude of this effect suggest progressive tolerance.
McLellanet al. (2005), Canada,(2)	Design of clinical trials.	31	29.8	NA	86.4	NA	male	Soldiers performing a control observation and reconnaissance vigilance task in the field.	200 mg of caffeine gum	It was concluded that caffeine-maintained vigilance and improved running performance during an overnight field operation for Special Forces personnel.
Ramos-Campo et al. (2019), Spain, (14)	Randomized and comparative crossover study design.	15	23.7	1.77	64.6	NA	male	Runners in mid-level events.	6 mg·kg-1 BW	Non-enhancement of 800 m running performance. Alteration in subjective sleep quantity and quality.

AUTHOR (YEAR), COUNTRY, (REFERENCE)	STUDY DESIGN	PARTICIPANTS	AGE	HEIGHT m	WEIGHT kg BMI (kg/m2) GENDER			PARTICIPANTS/ ACTIVITIES	CAFFEINE INTAKE COMPARED WITH PLACEBO	CONCLUSIONS
Sanchiset al. (2020), Spain, (21)	Design of clinical trials.	24	22.6	NA	NA	NA	male	Active young adults.	5 mg·kg-1 BW	While caffeine improved arousal vigilance during light and moderate exercise, additionally reducing lapses committed during moderate exercise, it did not affect executive vigilance.

The common feature of the studies reviewed is to determine whether acute ingestion of a caffeine-containing supplement may improve the performance of individuals. On the one hand, several studies have found positive ergogenic effects in tests following caffeine supplementation. Moreover, some studies have reported controversial results, often attributable to participants' caffeine habits (6). In fact, it is well known that people habitually gather often to talk, write, read, entertain themselves, and also spend time drinking coffee .

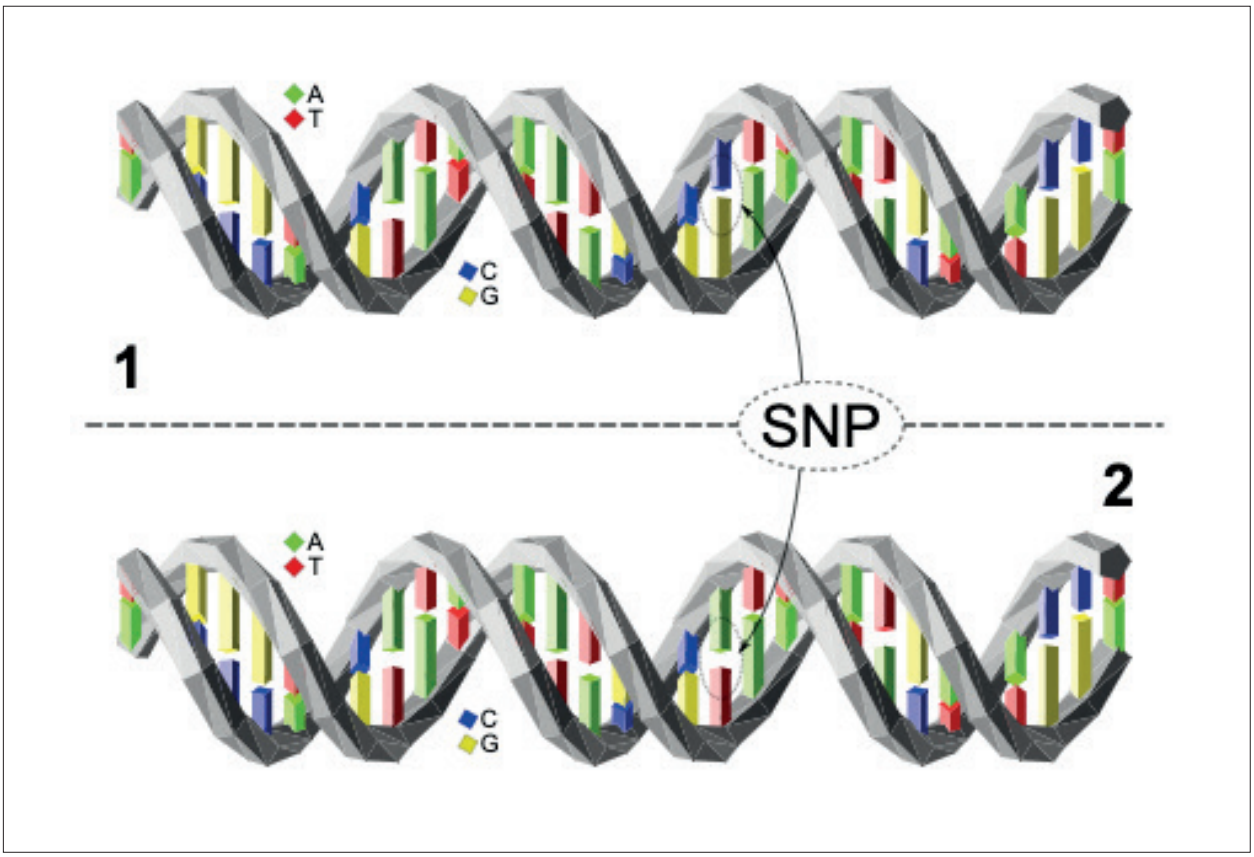
Figure 2. The pattern of manifestation of hereditary traits.



Since the interaction of an individual's genotype with the environment in which genes express themselves constitutes the phenotype, the combination of pairs of alleles that make up the genes for a given inherited character, such as eye colour determines the manifestation of a phenotype. In our species, there are two alleles for each gene, one of maternal origin and one of paternal origin. If the two alleles are identical then the individual is called homozygous, otherwise heterozygous for that gene. A given dominant

hereditary character is manifested thanks to a dominant allele that is also present only in heterozygote form and not necessarily only in homozygote form. Conversely, only when the recessive allele is in the homozygous form then a recessive character when manifested. Image by Darryl Leja, National Human Genome Research Institute (https://commons.wikimedia.org/wiki/File:Heterozygous.jpg), "Heterozygous", marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-US.

Figure 2. Single nucleotide polymorphisms.



According to the definition given by the U.S. National Library of Medicine, "Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among people. Each SNP represents a difference in a single element of DNA, called a nucleotide. For example, an SNP can replace the cytosine (C) nucleotide with the thymine (T) nucleotide in a certain stretch of DNA". The word polymorphism refers to various contexts and describes situations where something occurs in different forms. Our DNA is a structure made up of paired nitrogen molecules or bases that are responsible for its structure. About every 1000 fixed bases of individual DNA, there is a possible variation, and the element that changes refers to "SNP" (single nucleotide polymorphism). These polymorphisms play a role in inducing the specific susceptibility of the body's responses to internal (endogenous) and external (exogenous) stimuli. Therefore, knowing the individual-specific polymorphisms makes it possible, in terms of estimation, to assess the increase in specific risk compared to the general population. Image by David Eccles (gringer). Source: Single nucleotide polymorphism Facts

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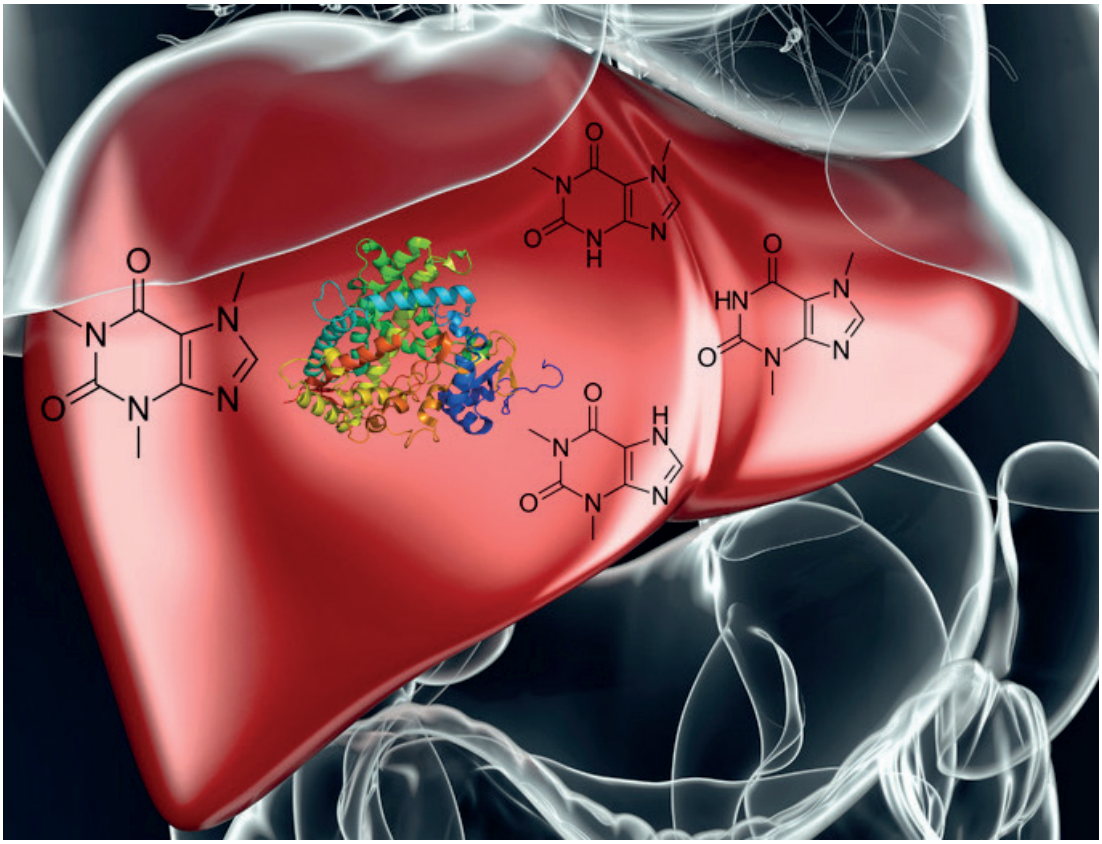
Not only caffeine habits but also the genetic profile of individuals has become a leading factor in the variability of people's response to caffeine (Figure 2). The focus has been on the CYP1A2 and ADORA2A genes, as certain polymorphisms explain the variability in both caffeine metabolism in the liver and signal transduction mechanisms in the nervous system (Figure 3) (6).

Caffeine metabolism. Some individuals assimilate caffeine faster than others (7). Caffeine metabolism is approximately 95% regulated by the enzyme cytochrome P450 1A2 (Figure 3). Cytochrome P450 belongs to a class of enzymes that catalyzes the oxidation-reduction reactions responsible for the metabolism of 75% of the drugs in the human body. When ingested, caffeine is rapidly absorbed through the gastrointestinal tract and is metabolized in the liver (8).

Figure 3. The cytochrome P450 oxidase enzyme system metabolizes caffeine (to the left) in the liver by the CYP1A2 isozyme (in the centre), into paraxanthine (84%), theobromine (12%), theophylline (4%) (clockwise on the right), and 1,3,7-trimethyl uric acid (1%, not shown in the figure).



Modified image; source: https://www.slon.pics/product/human-liver-3d-illustration/ "Human liver. 3D illustration" by 2022 slon. pics - free stock photos and illustrations, marked as public domain, licensing: 'Slon.pics free'.

The CYP1A2 gene has been shown to encode cytochrome P450-1A2, but a single nucleotide polymorphism, rs762551, within this gene affects the rate of caffeine metabolism (Table 3). Because individuals with the AA genotype at rs762551 produce more of the enzyme, they are "fast metabolizers" of caffeine. Conversely, individuals carrying the C allele, identified as "slow metabolizers," produce a lower amount of enzyme. Clinically, the lower caffeine clearance in "slow metabolizers" associated with recommended caffeine consumption may expose them to possible cardiovascular problems. This would not seem to be the case in "fast metabolizers" (6). In 2018, a study conducted on cyclists engaged in a 10 km time trial suggested that the CYP1A2 genotype of the athlete engaged in an endurance competition should be considered in deciding to use caffeine to improve performance (7). The investigation showed that a moderate dose of caffeine (4 mg·kg-1 BW, bodyweight) has an ergogenic effect only in AA genotypes. Another study conducted on cyclists engaged in a 40 km test produced similar results. The individuals involved in that study, homozygous for the A allele of the cytochrome P450 gene (CYP1A2), benefiting from optimal caffeine metabolism, had ergogenic clinical results from caffeine ingestion (9, 10). However, recent research did not fully support these conclusions (11). The study compared two groups of men trained for endurance activities. Thirteen of them carried the A allele of the single nucleotide polymorphism of the CYP1A2 gene (AA genotype), while nine carried the C allele (AC/CC genotype). The results of the tests performed produced no significant differences between the athletic performance of individuals with the AA genotype and those with the AC/CC genotypes. Thus, according to the results, the improvements in performance in endurance, jumping, and sprinting exercises induced by caffeine in these groups would not be significantly different. Ultimately, to date, it appears that the results are controversial. According to some studies, AA genotypes report a greater response to caffeine. In contrast, other studies show a better response to caffeine in C carriers. It would thus appear that the CYP1A2 polymorphism does affect caffeine metabolism but does not have an effect on the ergogenic response to caffeine (12).

Table 3. Influence of genetic variations in CYP1A2 on the ergogenic response to acute caffeine intake according to the studies reviewed.

GENOTYPES	RECOMMENDED ADMINISTRATION	MAIN BENEFITS	MAIN SIDE EFFECTS
Genotype AA "fast" metabolizers of caffeine.	From 3 to 9 mg·kg-1 BW, 60 minutes before activity.	Enhanced ergogenic effect.	Possible increased anxiety.
Genotype C "slow" metabolizers of caffeine.	Possibly increase caffeine intake and frequency of consumption.	Reduced ergogenic effect compared to the other genotype.	Insomnia.

Caffeine effects on the central nervous system (CNS). Typically, sportspeople ingest caffeine to improve athletic performance but also to increase alertness. The caffeine molecule is structurally similar to adenosine and therefore, at the CNS level, can bind to its receptors, acting as a competitive inhibitor of adenosine. Hence, adenosine plays a role in the CNS as a neuromodulator and in non-nervous tissue, accumulating and releasing under conditions of activity or stress (13). As a result, the ingestion of caffeine causes a delay in the onset of sleep and fatigue (14). Research has characterized four adenosine receptors, named A1, A2A, A2B, and A3. Respectively A1 and A2A adenosine receptors are both affected by polymorphisms which results in a different response to the caffeine stimulus (15).

Recent studies have demonstrated that the genetic profile of athletes has a great influence on

responses to the intake of this ergogenic aid (16). The ADORA2A gene encodes for the adenosine A2A receptor. The rs5751876 polymorphism in the ADORA2A gene influences the excitability of the nervous system and appears to have a directly modifying impact on the ergogenic effects of caffeine (Table 4). In summary, carriers of the C allele, namely those who do not improve performance after caffeine intake, belong to the category of "non-responders", otherwise known as "low caffeine sensitivity". On the contrary, subjects referred to as "responders", otherwise called "high caffeine sensitivity", benefit from caffeine intake as carriers of the T allele. However, once again the main findings of the conducted investigations are contradictory.

According to a 2015 study (17) in active women caffeine was found to be ergogenic for homozygotes of the T allele of the adenosine A2A receptor (ADORA2A). In contrast, a recent 2020 study on ergogenic responses to dietary caffeine supplementation showed that carriers of the C allele of ADORA2A (rs5751876) respond positively to caffeine supplementation (18). Thus, according to that study, individuals with the CT/CC genotype may benefit from acute caffeine supplementation to improve performance.

Table 4. Influence of genetic variations in ADORA2A on the ergogenic response to acute caffeine intake according to the studies reviewed.

GENOTYPES	RECOMMENDED ADMINISTRATION	MAIN BENEFITS	MAIN SIDE EFFECTS
Genotype TT "high" sensitivity to caffeine.	If anxiety sets in, reduce caffeine intake before the competition.	Enhanced ergogenic effect.	Increased diuresis, and excessive dynamism.
Genotype C "low" sensitivity to caffeine.	If the athlete needs to sleep well after training, reduce the dose of caffeine before the competition.	Reduced ergogenic effect.	Reduced sleep quality.

Caffeine effects on men and women. Research shows that women experience the same ergogenic response to caffeine as men. A study conducted in 2019 on the ergogenic effects of caffeine comparing both women and men engaged in endurance cycling trials, has corroborated the assertion above (19). The investigation involved triathletes, a group of volunteers consisting of eleven women and sixteen men, who were subjected to a balanced diet protocol that excluded foods and drugs that could affect caffeine metabolism, such as the bioactive furanocoumarins found in grapefruits. Participating women were voluntarily taking oral contraceptives independently of the study. Ultimately, the study found that taking 3 mg·kg-1 BW of caffeine improved endurance exercise performance in both women and men.

The same conclusions for anaerobic performance were reached by a recent study conducted in 2021. After ingesting an acute dose of 3 mg·kg-1 BW of caffeine, men and women were engaged in the Wingate Anaerobic Test (20).As is well known, it is a performance test in which the athlete pedals on an ergometer against a resistance set at a certain percentage of his or her body weight and at maximum effort for 30 seconds. It is a plain and effective test and, in short, makes it possible to assess an athlete's anaerobic capacity.

Returning to the study mentioned above, the researchers determined the extent of the ergogenic effect of caffeine on peak power gains and average cycling speed during the test. Overall, the similar ergogenic effect of caffeine in both genders would justify its use during anaerobic exercise (20).

Effects on cognitive skills. Research has investigated with great interest the effects of caffeine on both physical performance and alertness. Recent studies on alertness define it as having two different components: the arousal component of vigilance, defined as the ability to react rapidly to the appearance of stimuli in the environment for long periods (21), and the executive component of vigilance i.e., the ability to maintain attention to detect rare but critical events (22). For

example, consider the activity of both cycling or driving a car in the city during rush hour. Such activities require a lot of attention while driving, but also constant vigilance to avoid any unforeseeable situations due to urban traffic.

Similarly, several studies have investigated the ability of caffeine to stimulate the central nervous system mainly through interactions with adenosine receptors (23). In this connection, a study team from Auburn University in Alabama, U.S., carried out a study in 2016 to evaluate the effect of a supplement containing caffeine (100 to 300 mg/dose) on performance and fatigue in golf. Competitive golf requires a high level of cognitive and motor performance to be successful, and that investigation showed that caffeine reduces golf-specific fatigue translating into maintaining accuracy and improving overall golf performance (23). At about the same time, a group of researchers from the School of Applied Physiology at the Georgia Institute of Technology in Atlanta, U.S., had studied the level of attention and cognitive performance after exercise with and without caffeine in endurance-trained adults compared with sedentary adults. Following the experiments, the researchers argued that exercise can improve attention after a mentally demanding attention task, regardless of the participants' fitness status. Furthermore, when exercise is combined with caffeine ingestion (3 mg·kg-1 BW) compared with placebo, there would be greater benefits in the attention task with regard to accuracy, precision, and mental energy, further confirming the effects on cognitive skills (24).

Effects on military skills. Important insights into this issue come from the typical observation and reconnaissance activities that soldiers perform in the field. In short, military personnel usually work intensively during sentry services, states of emergency, radar or sonar monitoring in air or undersea reconnaissance services, etc. In these situations, individuals must perform quite complex cognitive tasks that may also require prolonged wakefulness (5). Recently, a systematic review by the Australian Department of Defense (25) evaluated the cognitive sphere-level benefits of a wide range of dietary supplements. These supplements were found to be potentially useful in optimizing the performance of higher-level mental functions that enable an individual to collect, store, and process information from the surrounding environment in a military context to adapt to it. Among the dietary supplements examined, caffeine, at a dose deemed appropriate of about 4 mg·kg-1 BW, appears to improve attention, memory, problem-solving ability, and logical reasoning in sleep-deprived adult subjects. This is a common condition during prolonged military operations when sleep opportunities are inadequate. In this context, ingestion of caffeine in different modes of administration, i.e., capsules, chewing gum, beverages, and coffee, may improve cognitive performance requiring attention, executive function, and speed of information processing.

Caffeine side effects. Ingesting a widespread and commonly used substance such as caffeine should require some care from both male and female athletes. Athletes should ingest the minimum recommended ergogenic dose to avoid unwelcome side effects. An important topic of study concerned the effects of taking incremental doses of caffeine on increasing muscle strength and the possible occurrence of side effects. A research group (26) implemented tests to evaluate the efficacy of ingesting placebo or caffeine at doses of 3 mg-kg-1 BW, 6 mg-kg-1 BW, and 9 mg-kg-1 BW. Muscle strength and power tests consisted of measuring barbell movement speed and muscle power during free-weight squat and bench press exercises with incremental loads. Study results showed a direct relationship between caffeine dose and ergogenic effect for all caffeine doses compared with placebo, while gastrointestinal problems, headaches, and insomnia appeared with doses of 6 mg-kg-1 BW or higher. At the highest caffeine doses of 9 mg-kg-1 BW, side effects remained up to 24 hours after the test. In contrast, a lower dose of caffeine (3 mg-kg-1 BW) prevented the appearance of unwanted side effects.

Caffeine tolerance. A research group investigated the progressively reduced effect of caffeine on athletic performance over days (27). In other words, they assessed caffeine tolerance. The researchers compared the effects of ingesting 3 mg·kg-1 BW per day of caffeine for 20 consec-

utive days versus placebo in participants performing the same exercise protocol consisting of the 15-second version of the Wingate Anaerobic Test. They initially found a significant increase in measured test performance during the first 2 weeks of caffeine ingestion. Then the change in performance measured when participants took caffeine did not differ significantly from placebo performance as the days passed. Overall, the response to acute doses of caffeine in subjects habituated to caffeine suggests the existence of a progressive tolerance to the benefits of caffeine on performance.

CONCLUSION

Although theory points to caffeine as a CNS stimulant and research ascribes ergogenic properties to caffeine, both contexts rightly claim to improve performance and promote a state of alertness, undoubtedly benefiting from targeted caffeine intake. In the literature, caffeine intake has been associated with improved performance parameters in the sports context. In many cases, the dose and time of intake may be associated with the effectiveness of the desired effect. Furthermore, there is some evidence that caffeine can positively influence cognitive components and alertness. These results suggest that caffeine may improve the outcome of psychophysical engagement, especially in specialised fields such as the military, disaster relief or emergency situations, generally speaking. In conclusion, all the aspects discussed in this paper would be a fruitful area for further work. If the debate is to be moved forward, a better understanding of the dosage and timing of caffeine needs to be developed.

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